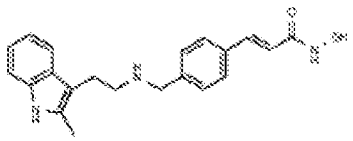
DETAILED ACTION

Applicant's response, received 1/31/08, to the restriction/election requirements, mailed 1/2/08, electing invention I, midostaurin as the FLT-3 inhibitor species, AMl as the disease species, and the below compound as the HDAI compound species, is acknowledged:



Applicant's statement that claims 1-20 read on the elected species is acknowledged and made of record.

Claims 1-9 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected claims.

Applicant's preliminary claim amendment filed 2/8/06 is also acknowledged.

Status of the Claims

Claims 1-23 are currently pending in this application.

Claims 21-23 are withdrawn for examination purposes for being directed to non-elected subject matter.

Restriction/Election

Applicant's response to the restriction/election requirements is considered to be without traverse as applicant has failed to proffer any traversal argument pointing out any errors in the requirements.

The restriction/election requirements are made final.

Objection to the Claims

Claim 4 is objected to for reciting the language "a number from and including 0 to and including 4." It is suggested that this objection may be overcome by amending the claims to delete said term and replace it with the term "a number from 0 to 4."

Rejection under 101

35 USC 101 reads as follows

> Whoever invents or discovers any new and useful process, machine, manufacturer, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 15-20 are rejected under 35 USC 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e. results in a claim which is not a proper process claim under 35 USC 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd. V. Brenner,* 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

LACK OF WRITTEN DESCRIPTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH:

Claims 1-20 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification discloses chemicals which meet the written description and enablement provisions of 35 USC 112, first paragraph. However, claims 1-20 are directed to encompass undisclosed prodrugs and derivative compounds which only correspond in some undefined way to specifically instantly disclosed chemicals. In particular claim 1 recites the term “prodrug thereof,” while claim 3 recites the term “staurosporine derivative.” None of the undisclosed compounds meet the written description provision of 35 USC § 112, first paragraph, due to lacking chemical structural information for what they are and chemical structures are highly variant and encompass a myriad of possibilities. The specification provides insufficient written description to support the genus encompassed by the claim.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that

[he or she] invented what is claimed." (See Vas-Cath at page 1116.).

With the exception of the above specifically disclosed chemical structures, the skilled artisan cannot envision the detailed chemical structure of the encompassed compounds, analogs, etc., regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The chemical structure itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmacentical Co. Ltd., 18 USPQ2d 1016. In Fiddes v. Baird, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.Finally, University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that:

> ...To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." *Lockwood v. American Airlines, Inc.* , 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); *In re Gosteli* , 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using

"such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." *Lockwood* , 107 F.3d at 1572, 41 USPQ2d at 1966.

Therefore, only the disclosed chemically structurally defined chemicals, but not the full breadth of the claim(s) meet the written description provision of 35 USC § 112, first paragraph. The species specifically disclosed are not representative of the genus because the genus is highly variant. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC § 112 is severable from its enablement provision. (See page 1115.)

Claim rejections – 35 USC 112 – Second Paragraph

The following is a quotation of the second paragraph of 35 USC 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term “FLT-3” renders the claimed subject indefinite. For example, claims 1, 3, 3, 15, 17, 18, and 20 recite said term but fail to state the full meaning of the term at the first occurrence the term is recited in the claim set. This limitation is vague and indefinite because it is not clear what “FLT-3” means. It is suggested that this specific rejection may be overcome by either replacing the term “FLT-3” with the full name or,

alternatively, amend the claims by inserting the full name in parenthesis at the first occurrence of the term “FLT-3” in the claim set.

Dependent claims 2, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 16, and 19 are rejected for the same reason for failing to correct the deficiency of the claim from which they depend.

Claim 7 recites the term “HDAI,” but fails to state the full meaning of the term at the first occurrence the term is recited in the claim. To the extent that the full meaning of the term is not recited in the claim from which said claim depends renders the subsject matter indefinite for lack of a proper antecedent basis.

Dependent claims 8, 9, and 10 are rejected for the same reason for failing to correct the deficiency of the claim from which they depend.

Claims 15-20 recite the term “ Use,” but, since the claims do not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claim rejections – 35 USC 103(a)

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-20 are rejected under 103(a) as being unpatentable over Remiszewski et al. (US Patent 6,552,065), in view of Verner et al. (US Patent 7,276,612) and Griffin et al. (US Patent Application Pub. No. 2005/0020570 A1).

For purposes of this rejection, claims 15-20 (i.e. the Use claims) are construed as method of treatment claims.

Remiszewski et al. teach that inhibitors of HDA have been studied for their therapeutic effects on cancer cells, however, there remains a need for an active compound that is suitable for treating tumors, including cancerous tumors, that is highly efficacious and stable (col. 1, lines 14-40). Remiszewksi et al. teach that even though butyric acid and its derivatives, including sodium phenylbutyrate, have been reported to induce apoptosis in vitro in human colon carcinoma, leukemia and retinoblastoma cell lines, these agents are not useful pharmacological agents because they tend to be

metabolized rapidly and have a very short half-life in vivo (col. 1, lines 14-40). Although Remiszewski reference exemplify applicant's elected HDAI compound and leukemia (cols. 24-25, Example P3; see also cols. 115-116, Compound 200), it does not expressly teach AML i.e. applicant's elected cancer species. In addition,,Remiszewski et al.do not teach FLT3 inhibitors alone or in combination with HADI's.

Verner et al. (US Patent 7,276,612) teach that HDAIs are useful for treating various conditions, including AML, and may be co-administered with other therapeutic agents (col. 49, line 20-35; col. 50, line 62 to col. 51, line 15; and col. 58, line 51 to col. 59, line 10). Verner et al. do not teach the instant claimed combination of a FLT3 inhibitor plus a HDAI.

Griffin et al. (US Patent Application Pub. No. 2005/0020570 A1) teach that aberrant expression of the FLT3 gene has been documented in both adult and childhood leukemias, including acute myeloid leukemia (AML), AML with trilineage myelodysplasia (AMLUTMDS), acute lymphoblastic leukemia (ALL), and myelodysplastic syndrome (MDS)(para 0252). Griffin et al. teach that Midostaurin (or PKC42) that FLT-3 possesses inhibitory properties that render it particularly useful as an inhibitor of FLT-3 receptors and especially in the treatment of leukemias and myelodysplastic syndromes (paras 0232-0235).

Based on the teaching of Griffin et al. that Midostaurin (or PKC42) possesses inhibitory properties that render it particularly useful as an inhibitor of FLT-3 receptors, especially in the treatment of leukemias and myelodysplastic syndromes (paras 0232-0235), someone of skill in art would have been motivated to combine the teachings of

the above cited references to create the instant claimed inventive concept of combining and HDAI inhibitor with an FLT-3 inhibitor to treat AML.

Thus, someone of skill in the art at the time the instant invention was made would have found it obvious to create the instant claimed invention with reasonable predictability.

Relevant Art of Record

The below cited art made of record and relied upon is considered pertinent to applicant's invention with respect to the general state of the art for treating AML.

Comment [C1]:

Lee et al. teach methods of treating AML comprising administering a combination of at least three drugs (Lee et al. Parallel Phase I Studies of Daunorubicin Given With Cytarabine and Etoposide With or Without the Multidrug Resistance Modulator PSC-833 in Previously Untreated Patients 60 Years of Age or Older With Acute Myeloid Leukemia: Results of Cancer and Leukemia Group B Study 9420. Journal of Clinical Oncology. 1999. 17(Issue 9): 2831-2839).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Charlesworth Rae whose telephone number is 571-272-6029. The examiner can normally be reached between 9 a.m. to 5:30 p.m. Monday to Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward, can be reached at 571-272-8373. The fax phone

number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR.

Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http:pair-direct.uspto.gov. Should you have any questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 800-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

9 April 2008

Examiner /C.R./

/Brian-Yong S Kwon/

Primary Examiner, Art Unit 1614